Gemcitabine combined with oxaliplatin is safe and effective in patients with previously untreated advanced pancreatic adenocarcinoma

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SUMMARY

Aim — The aim of this study was to determine the safety and the efficacy of a gemcitabine/oxaliplatin combination (GEMOX) as first line therapy in patients with metastatic or unresectable locally-advanced pancreatic cancer.

Patients and methods — Patients received gemcitabine 1000 mg/m² as a 10-mg/m²/min infusion on day 1 followed on day 2 by oxaliplatin 100 mg/m² as a 2-hour infusion, each cycle being given every 2 weeks. All patients had measurable disease and histological diagnosis before inclusion. Patients were treated until progression or for 12 cycles in the absence of progression. Tumor lesions were assessed by computed tomography scan every 4 cycles.

Results — Between January 2001 and January 2003, 32 patients were eligible for the study. The objective response rate (OR) was 28.1% with a 12.5% complete response rate (CR). Median progression-free survival and median overall survival were 7 and 9 months, respectively. Median overall survival for patients with metastatic disease and locally-advanced disease were 7 and 25 months, respectively (P < 0.0007). Eleven patients were alive at 1 year (34.4%), six at 2 years (18.8%) and two at 3 years (6%). Fourteen (43.8%) of 32 patients experienced a clinical benefit response.

Conclusion — These results support the safety, the antitumor activity and the possibility of durable responses of the GEMOX regimen in patients with locally-advanced disease.

RÉSUMÉ

L’association Gemcitabine/Oxaliplatine est bien tolérée et efficace en première ligne thérapeutique chez les malades atteints d’un adénocarcinome pancréatique

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But — Le but de cette étude était de déterminer la tolérance et l’efficacité de l’association gemcitabine/oxaliplatine, en première ligne thérapeutique, chez des malades porteurs de tumeurs du pancréas métastatiques ou loco-régionalement évolutées.

Malades et méthodes — Les malades ont bénéficié de l’administration de gemcitabine à la dose de 1000 mg/m² délivrée en 10/mg/m²/min au jour 1 suivie au jour 2 par l’administration en 2 heures d’oxaliplatine à la dose 100 mg/m²2. L’intervalle entre chaque cycle était de 15 jours. Tous les malades avaient une tumeur du pancréas histologiquement prouvée avant l’inclusion dans l’étude. Les malades ont été traités jusqu’à progression de la maladie ou pendant 12 cycles en l’absence de progression. Un bilan tomodensitométrique était réalisé tous les 2 mois pour évaluer l’évolution de la maladie.

Résultats — Entre janvier 2001 et janvier 2003, 32 malades ont été éligibles pour entrer dans l’étude. Le taux de réponse objective a été de 28,1 % avec 12,5 % de réponse complète. La survie sans progression et la survie globale de l’ensemble des malades ont été respectivement de 7 et 9 mois. Cependant, la survie globale était significativement plus importante pour les tumeurs loco-régionalement évolutées par rapport au tumeurs métastatiques (25 mois versus 7 mois, P < 0,0007). Onze malades étaient en vie à 1 an (34,4 %), six à 2 ans (18,8 %) et deux à 3 ans (6 %). Quatorze malades (43,8 %) ont présenté un bénéfice clinique selon les critères d’Anderson.

Conclusion — Ces résultats confirment la bonne tolérance de l’association gemcitabine/oxaliplatine et suggèrent que cette association peut avoir une activité anti-tumorale durable pour les tumeurs loco-régionalement évolutées.

Introduction

Pancreatic adenocarcinoma is the fifth most common cause of cancer death in western countries [1]. Only 10 to 20% of patients undergo surgery with curative intent [2]. Most patients with pancreatic cancer present with obvious metastases or unresectable locally-advanced disease and, consequently, have extremely poor prognosis. The median survival for these patients ranges from 3 to 6 months in randomized studies. However, three randomized trials have proven that chemotherapy provides a significant benefit in median survival compared with best supportive care [3-5]. In 1997, Burris reported a phase III randomized trial comparing gemcitabine, a cytidine analogue, with 5 FU in naive patients with advanced pancreatic cancer [6]. The results of this study suggested that patients receiving gemcitabine had an improved clinical benefit response compared with patients receiving 5 FU (24% versus 5%). Moreover, there was a striking difference in survival between the two arms since 1-year survival was 18% for gemcitabine as compared with 2% for 5 FU. Therefore, gemcitabine has become a reference chemotherapeutic agent for palliation in advanced and symptomatic pancreatic cancers. Gemcitabine is an inactive prodrug that acts
by intracellular activation into phosphorylated metabolites. An infusion rate of 10 mg/m²/min was found to be optimal to achieve the best conversion rate of active phosphorylated gemcitabine [7] and seems superior as compared with a 30-minute infusion. Oxaliplatin is a diamino-cyclohexane containing-platinum active in several solid tumor types. In vitro studies have showed a cytotoxic effect of oxaliplatin against pancreatic cancer cell lines [8]. Like cisplatin, oxaliplatin reacts with DNA, forming primary lesions that block DNA replication and transcription. Moreover, apoptosis induction seems to be an important factor in the mechanism of action of oxaliplatin [9]. The rationale for the use of gemcitabine/oxaliplatin combination is based on biological data. Gemcitabine-oxaliplatin combination displayed supra-additive effect in human colon-cancer cell lines with an optimal sequence-dependent synergy when tumor cells were exposed to gemcitabine first and then to oxaliplatin 24 hours later [10]. Furthermore, oxaliplatin/gemcitabine combination was superior in vitro to cisplatin/gemcitabine combination [10].

We undertook a phase II study to determine the activity and the safety of the gemcitabine/oxaliplatin association (GEMOX regimen) in naïve patients with locally-advanced or metastatic pancreatic cancer.

**Patients and methods**

**Patients**

Eligible patients had histologically confirmed non-resectable pancreatic adenocarcinoma (ie, locally-advanced or metastatic disease). The other inclusion criteria consisted of a performance status ≤ 2, as assessed for each patient prior to treatment initiation and after each course of chemotherapy using the World Health Organization scale, an age ≤ 75 years, and a life expectancy of at least 3 months. Prior to each course of chemotherapy, a laboratory panel was conducted for each patient: leukocytes > 4000/µL, platelets > 100,000/µL, BUN < 30 mg/dL, creatinine < 1.5 mg/dL, and total bilirubin < 1.5 mg/dL. Patients with tumors of the ampulla of Vater and cholangiocarcinoma were not eligible. This study was performed according Helsinki criteria and a written informed consent was obtained from each patient.

**Chemotherapy regimen**

All the patients received gemcitabine and oxaliplatin-based chemotherapy (GEMOX) as followed: gemcitabine 1000 mg/m² in a 10 mg/m²/min infusion on D1, followed on D2 by oxaliplatin 100 mg/m² in a 2-hour infusion every two weeks [11]. Dose reductions and treatment postponements were conducted as a function of clinical toxicity and the laboratory test results. Treatment was deferred for one week in the event of grade 3/4 toxicity, in line with the World Health Organization criteria. Chemotherapy was given for a total of 12 cycles in the absence of toxicity or until progression. Radiotherapy alone was authorized in case of stabilisation or response after chemotherapy.

**Response assessment**

All patients had measurable lesions and underwent abdominal CT-scan prior to chemotherapy initiation. The response was evaluated every 2 months by CT-scan. The objective responses were evaluated according to the International Union Against Cancer’s recommendations. A complete response (CR) was defined as total disappearance of all measurable lesions over at least 4 weeks, while a partial response (PR) was defined as a decrease of at least 50% in the measurable tumor mass. Stable disease (SD) was defined as a decrease of less than 50% in tumor mass or a progression of less than 25%. Progressive disease (PD) was defined as an increase in tumor mass greater than 25%. Clinical benefit was evaluated according to the Andersen’s criteria [6, 12].

**Statistical analysis**

Sample size was calculated according to a single-stage phase II study [13]. GEMOX would be considered unsuccessful if the objective response rate was 5% or less, and it would be considered active enough to pursue further treatment if the objective response rate was 20% or greater. With 30 subjects, power would be 85% to detect a 20% objective response rate with a 5% alpha error.

Overall survival and progression free survival were calculated according to the Kaplan-Meier product-limit estimates and compared by the logrank test. A P value < 0.05 was considered significant.

**Results**

**Patient’s characteristics**

Thirty-two patients with advanced pancreatic adenocarcinoma were prospectively included in the study from January 2001 to January 2003. Median follow-up was 24 months (range: 3-40). The patients’ characteristics are summarized in table I. The study population consisted of 17 men and 15 women, mean age 65 years (range: 40-75). The performance status was ≤ 1 for most of the patients (56.3%). Hepatic metastases were present in 19 cases (59.4%). Peritoneal carcinomatosis and bone metastasis without hepatic metastasis were present in 2 out of 32 patients (6.2%) and 11 of the 32 patients had locally-advanced disease (34.4%).

**Treatment characteristics**

Table II shows the number of courses of chemotherapy and the mean oxaliplatin and gemcitabine doses received by the patients. The median number of chemotherapy courses received by patients was 9.6 equivalent to a mean duration of treatment of 4.5 months; a total of 308 cycles were administered every two weeks. Chemotherapy had to be postponed for 18 patients (56.3%), due to hematological (neutropenia or thrombopenia) or neurological toxicity. Treatment was deferred for one week for 11 patients and for more than one week for 7 patients.

**Toxicity**

Table III shows the toxicity occurring during treatment. The toxicity observed was grade 1/2 in the majority of cases. Grade 3/4 toxicity was infrequent and mainly consisted of thrombocytopenia (28% of patients in 3.5% of cycles), neutropenia (12.5% of patients in 1.3% of cycles, with 3.1% of febrile neutropenia) and pain.

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>17/15</td>
</tr>
<tr>
<td>Median age (years) [range]</td>
<td>65 [40-75]</td>
</tr>
<tr>
<td>Disease at presentation</td>
<td></td>
</tr>
<tr>
<td>Locally-advanced</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>21 (65.6)</td>
</tr>
<tr>
<td>Site of metastases</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>19 (59.4)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Bone</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>OMS performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>1</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>2</td>
<td>14 (43.7)</td>
</tr>
</tbody>
</table>
neurotoxicity (28% of patients and for all these patients after cycle 7). No treatment-related deaths were observed.

**Tumor response and survival (table IV)**

The objective response rate was 28.1%, with complete response in 4 cases (12.5%). Stabilization of disease occurred in 50% of patients. For all patients, with a median follow-up of 24 mois, median progression-free survival was 7 months and median survival was 9 months. Median survival for patients with locally-advanced disease and for metastatic disease was 25 and 7 months, respectively (P < 0.0007) (figure 1). The survival rate was 34.4%, 18.8% and 6% at 1 year, 2 years and 3 years, respectively. In addition, fourteen (43.8%) of 32 patients experienced a clinical benefit response.

Four patients had complete response to GEMOX regimen, of which 3 had locoregional disease at inclusion and 1 with liver metastasis. For these patients, median survival was 25 months. Two patients had complete remission after 4 cycles, one patient after the 8th cycle and one after the 12th cycle. Three patients with locally-advanced disease underwent laparotomy, resection was performed in only one patient because two patients had fibrosis and arterial envolvement who prevented resection. The histopathological study showed a complete response for the resected patient and for one patient with fibrosis. The two non-resected patients developed recurrences. One patient had local recurrence 5 months after complete remission that was treated by continuous infusion of 5-FU and radiotherapy and then by 3rd-line chemotherapy combining taxol and capecitabine. The second patient developed hepatic metastasis 8 months after complete remission and was treated by 2nd-line chemotherapy with capecitabine and taxol.

### Discussion

Pancreatic cancer is one of the most lethal malignancies that oncologists encounter. Gemcitabine at dose of 1000 mg/m² in a weekly 30-minute infusion has evolved as standard therapy in advanced pancreatic cancer since the demonstration of improvements in survival and clinical benefit. However, this treatment motivates many attempts to provide better palliative treatment in this indication. Our study was performed to evaluate the efficacy of gemcitabine and oxaliplatine as first line chemotherapy for patients with unresectable metastatic or locally-advanced adenocarcinoma of the pancreas. In our study a 10 mg/m²/min gemcitabine schedule was chosen based on its better activity compared with 30-minute infusion [7]. Recently, Alberts at al. have reported a phase II study using a combination of oxaliplatin and gemcitabine with moderate activity [14]. This difference may be due to the use of a non-optimate schedule of chemotherapy: oxaliplatin was given on day 1 at dose of 100 mg/m² and gemcitabine on day 1 and 8 at dose of 1000 mg/m² every three weeks [14]. In this way, dose intensity of oxaliplatin was significantly reduced.

GEMOX regimen was well tolerated. In our study, grade 3-4 toxicity was experienced in 28% concerning thrombocytopenia
REFERENCES


